61. The method of claim 60 wherein said anthracycline is doxorubicin.

62. The method of claim 60 wherein said anthracycline is ruboxyl.

REMARKS

Claims 1-62 are pending in this application. Claims 1-31 were presented for examination at the time of filing the present § 371 application, but the Examiner apparently only examined claims 1-25. Claims numbered 1-25 were present in the international application as filed. In response to the Examiner's Written Opinion mailed September 13, 1999, a timely Response Under Rule 66.3 was filed on October 13, 1999, including (a) substitute sheets for amending pages 2, 10-12, 14, 16-18, 20, and 24-26 of the specification and (b) substitute sheets 30-32 for amending the claims such that a total of 31 claims were presented for international preliminary examination. A first International Preliminary Examination Report (IPER) was mailed on February 4, 2000, which did not acknowledge or consider the Response Under Rule 66.3 nor the amended claims and specification. After this oversight was brought to the PTO's attention in a letter mailed February 10, 2000, a second IPER was mailed on March 20, 2000, which did acknowledge and take into

account the amended claims and specification. The present § 371 application was filed on March 23, 2000, which was before the second IPER was received in the office of the undersigned attorney. Therefore, the IPER that was mailed to the PTO with the present § 371 application was the first IPER. However, a copy of the Response Under Rule 66.3 and the substitute sheets for amending the specification and claims did accompany the present application. Therefore, it is respectfully submitted that claims 1-31 were in the application at the time of filing and should have been considered by the Examiner when preparing the Office Action mailed August 1, 2001.

New claims 32-62 are presented herein. Claims 32-33, which are dependent on independent claim 24, relate to micellar drug carriers comprising AB-diblock copolymers. Support for these claims is found at pages 1-2 of the specification. New claims 34-35, which are dependent on independent claim 1; new claims 36-37, which are dependent on independent claim 9; and new claims 38-39, which are dependent on independent claim 16, also relate to micellar drug carriers comprising AB-diblock copolymers. New claims 40-45 have support in claims 1-8. New claims 46-50 have support in claims 9-15. New claims 51-56 have support in claims 16-23. New claims 57-62 have support in claims 24-31. Therefore, no new matter is added to the application by virtue of new claims.

The Examiner indicated that claims 3, 4, 11, 12, 19, and 20 were objected to as dependent on a rejected claim. New independent claims 40, 46, and 51 are intended to be similar in scope to claims 3, 11, and 19, respectively. New independent claim 57 is intended to be similar in scope to claim 26, which in turn is similar in scope to claims 3 and 19.

The application fee paid at the time of filing of the present application included the fees for one (1) excess independent claim and eleven (11) excess total claims. The new claims submitted herein comprise 4 new independent claims and 31 new claims. A check in the amount of $439.00 is enclosed herewith in payment for these claims. This amount is calculated as follows:

4 x $40 = $160.00

31 x $9 = $279.00

Total $439.00

The Commissioner is hereby authorized to charge any additional fees or credit any overpayment in connection with this response to Deposit Account No. 50-0836.

Abstract

The Examiner alleged that this application does not contain an abstract as required by 37 C.F.R. § 1.72(b). The Examiner further commented that an abstract on a separate sheet is required.

37 C.F.R. § 1.495 states that when entering the national stage in the U.S. as an elected office, the applicant shall furnish a copy of the international application unless it has been previously communicated by the International Bureau or unless it was originally filed in the USPTO. This application is an application filed under 35 U.S.C. § 371. The international PCT application was originally filed in the USPTO. In the international stage of the PCT application, the U.S. was elected prior to the expiration of 19 months from the priority date, thus making the USPTO an elected office. Therefore, it is not necessary for the applicants to provide an additional copy of the international application. Further, the PCT application as filed contained an abstract on a separate sheet under the heading "Abstract of the Disclosure." Therefore, it is respectfully submitted that the applicants complied with requirements of 37 C.F.R. § 1.72(b) at the time of filing of this § 371 application. The PTO is in possession of the abstract contained in the PCT application, therefore, it is respectfully requested that the Examiner recognize the "Abstract of the Disclosure" contained in the corresponding international application as the abstract of the present national stage application.

Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 1-2, 5-10, 13-18, and 21-25 were rejected under 35 U.S.C. § 112, first paragraph, because the specification allegedly does not provide reasonable enablement for any "micellar drug" with a hydrophobic core.

In the first instance, Applicants have not claimed a "micellar drug" having a hydrophobic core. Applicants assume that the Examiner meant to refer to the "micellar drug carrier" with a hydrophobic core referred to in the specification and claims.

The question of adequate and enabling support is a legal issue, and thus is independently reviewed on appeal. In re Vaeck, 20 U.S.P.Q.2d 1438, 1444 (Fed. Cir. 1991). Numerous decisions by the Federal Circuit and the CCPA state that, because the specification is directed to those having ordinary skill in that art, it is not necessary to disclose what is already known in the art. E.g., Hybritech Inc. v. Monoclonal Antibodies, Inc., 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986) ([A] patent need not teach, and preferably omits, what is well known in the art."); In re Howarth, 210 U.S.P.Q. 689, 691-92 (C.C.P.A 1981).

It is well established that a disclosure may be sufficient to enable one having ordinary skill in the art to practice the invention even though a certain amount of reasonable experimentation may be required. White Consolidated Indus. v. Vega Servo-Control, 218 U.S.P.Q. 961, 963 (Fed. Cir. 1983); W.L. Gore &

Assocs. v. Garlock, Inc., 220 U.S.P.Q. 303, 315 (Fed. Cir. 1983). The determination of any and all micellar drug carriers that will be efficacious when employed according to the instant invention as disclosed falls within this parameter.

While, according to the above decisions, undue experimentation should not be required, the question arises as to what constitutes "undue experimentation." This question is well answered by the Board of Appeals in the case of Ex parte Jackson, as follows:

> The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art. The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed.

Ex parte Jackson, 217 U.S.P.Q. 804, 807 (PO Bd App. 1982) (citations omitted).

When rejecting claims based on § 112, first paragraph, it is incumbent upon the Examiner to advance acceptable reasoning inconsistent with enablement. In re Strahilevitz, 212 U.S.P.Q. 561, 563 (CCPA 1982). Perhaps this requirement is best stated in In re Marzocchi, wherein the court stated:

> It is incumbent upon the Patent Office, whenever a rejection of this basis is made, to explain why it doubts the truth or accuracy of any statement made in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise,

> there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure.

In re Marzocchi, 169 U.S.P.Q. 367, 370 (CCPA 1971) (emphasis in original).

It has been consistently held that merely pointing out breadth in claim terminology was not enough and that a party asserting lack of compliance with 35 U.S.C. § 112, first paragraph, had the burden of presenting cogent technical reasoning or objective evidence to support its position regarding enablement. See Horton v. Stevens, 7 U.S.P.Q. 1245 (PTO Bd. App. & Int. 1988).

Applicants respectfully submit that the Examiner's reason for rejecting claims under Section 112, first paragraph, amounts to an allegation that the claim terminology is too broad. It is respectfully submitted that the Examiner has not met his burden of providing cogent technical reasoning or objective evidence as to why the claim terminology is allegedly too broad. In fact, the reasons given by the Examiner for the alleged lack of enablement are mere unsupported conclusions without any cogent technical reasoning or objective evidence provided to uphold such conclusions.

The Examiner alleged: "Applicants only disclose poloxamers. No other carrier is disclosed." This is incorrect. Applicants disclosed micellar drug carriers having hydrophobic cores (page 6, lines 3-4). It is also disclosed that these micelles have a

spherical core-shell structure with a hydrophobic block forming the core of the micelle and one or more hydrophilic blocks forming the shell (page 1, line 32, to page 2 line 1). Further, the specification discloses that the micellar drug carriers can be AB-diblock copolymers, such as poly(L-amino acid)-co-poly(ethylene oxide), or ABA-triblock copolymers, such as PEO-PPO-PEO (page 2, lines 3-18).

Moreover, the specification describes how a person skilled in the art can determine whether or not a particular drug carrier forms micelles in an aqueous environment (page 10, line 15, to page 10, line 31). Still further, the specification describes how a person skilled in the art can determine whether a drug partitions to the hydrophobic core of a micellar drug carrier, e.g., Example 1). Therefore, it is respectfully submitted that the specification discloses how a person skilled in the art could perform routine experiments for determining whether a particular drug carrier meets the limitations set out in the claims. It is further respectfully submitted that the specification provides a reasonable amount of guidance concerning the direction in which experimentation should proceed to enable the determination of how to make and use the invention as claimed. Therefore, no undue experimentation would be needed to enable a person skilled in the art to make and use the presently claimed invention.

Moreover, micellar drug carriers are well known in the art. For example, enclosed are copies of the following articles and abstracts:

1. M. Yokoyama, Polymeric micelles for Drug Delivery: Their Strategy and Perspective, 7th Int'l Symp. On Recent Advantages in Drug Delivery Systems 99-102 (1995) (discusses micellar AB block copolymers, including poly(ethylene glycol)-poly(aspartic acid));
2. G.W. Kwon et al., Physical Entrapment of Adriamycin in AB Block Copolymer Micelles, 12 Pharmaceutical Research 192-915 (1995) (discusses poly(ethylene oxide-co-β-benzyl L aspartate; PEO-PBLA));
3. G.S. Kwon et al., Block Copolymer Micelles as Vehicles for Hydrophobic Drugs, 2 Colloids and Surfaces B: Biointerfaces 429-434 (1994) (discusses micellar AB block copolymers, namely PEO-PBLA);
4. E.V. Batrakova et al., Anthracycline Antibiotics Non-covalently Incorporated into the Block Copolymer Micelles: *In Vivo* Evaluation of Anti-cancer Activity, 74 Br. J. Cancer 1545-1552 (1996) (discusses PEO-PPO-PEO block copolymers);
5. M. Yokoyama et al., Toxicity and Antitumor Activity against Solid Tumors of Micelle-forming Polymeric Anticancer drug and Its Extremely Long Circulation in

Blood, 51 Cancer Research 3229-3236 (1991) (abstr.; discusses poly(ethylene glycol)-poly(aspartic acid) micellar block copolymer);

6. M. Yokoyama et al., Characterization and Anticancer Activity of the Micelle-forming Polymeric Anticancer Drug Adriamycin-conjugated Poly(ethylene glycol)-Poly(aspartic acid) Block Copolymer, 50 Cancer Research 1693-1700 (1990) (abstr.; discusses poly(ethylene glycol)-poly(aspartic acid) micellar block copolymer);

7. G. Kwon et al., Micelles Based on AB Block Copolymers of Poly(ethylene oxide) and Poly(β-benzyl L-aspartate), 9 Langmuir 945-949 (1993) (abstr.; discusses PEO-PBLA);

8. X. Zhang et al., An Investigation of the Antitumour Activity and Biodistribution of Polymeric Micellar Paclitaxel (40 Cancer Chemother. Pharmacol. 81-86 (1997) (abstr.; discusses poly(DL-lactide)-block-methoxy polyethylene glycol micelles);

9. S.B. La et al., Preparation and Characterization of the Micelle-forming Polymeric Drug Indomethacin-incorporated Poly(ethylene oxide)-poly(beta-benzyl L aspartate) Block Copolymer Micelles, 85 J. Pharm. Sci. 85-90 (1996) (abstr.; discusses PEO-PBLA);

10. S.E. Dunn et al., Polystyrene-poly(ethylene glycol) (PS-PEG2000) Particles as Model Systems for Site Specific

Drug Delivery. 2. The Effect of PEG Surface Density on the In Vitro Cell Interaction and In Vivo Biodistribution, 11 Pharm. Res. 1016-1022 (1994) (abstr.; discusses polystyrene-poly(ethylene glycol) particles);

11. G.S. Kwon et al., Biodistribution of Micelle-forming Polymer-drug Conjugates, 10 Pharm. Res. 970-974 (1993) (abstr.; discusses PEO-poly(aspartic acid) micelles).

These articles and abstracts show that micellar drug carriers having hydrophobic cores are well known in the art from a date prior to the filing date of the present application. Such micellar drug carriers include, but are not limited to, poloxamers.

In view of the above, Applicants respectfully submit that they have met the requirement of 35 U.S.C. § 112, first paragraph, in disclosing their invention sufficiently to enable one having ordinary skill in the art to make and use the invention without undue experimentation. Withdrawal of the rejection is respectfully requested.

Conclusion

Should the Examiner deem it advisable to conduct a telephone interview for any reason, the undersigned attorney would be most agreeable to receiving a telephone call to expedite the prosecution of the application.

For the reasons given above, Applicants respectfully request reconsideration and allowance of Claims 1-62 and passage of this application to issue.

DATED this 30th day of October, 2001.

Respectfully submitted,

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